REMARKS

Claims 1-11, 13 and 14 currently appear in this application. The Office Action of November 14, 2005, has been carefully studied. These claims define novel and unobvious subject matter under Sections 102 and 103 of 35 U.S.C., and therefore should be allowed. Applicants respectfully request favorable reconsideration, entry of the present amendment, and formal allowance of the claims.

REJECTIONS UNDER 35 U.S.C. 112

Claims 1-3 and 6-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification is said to be enabling only for metal ions that have antimicrobial activity.

This rejection is respectfully traversed. The claims have been amended to recite that the metal ions are pharmaceutically acceptable polyvalent metal ions. Support for this amendment can be found in the specification as filed at paragraphs 32-33.

As described in the specification cited above, the metal ions that are delivered are specifically pharmaceutically acceptable metal ions that block the calcium cascade by swamping it. These polyvalent ions take the place of calcium ions, so that the cascade is interrupted. Calcium acts as a trigger for the kinases that produce the mucous from

goblet cells and sub-mucosal glands associated with rhinitis, and thus produces probable positive charges in mucociliary clearance. The other ions block the kinases by attaching to the kinases but not triggering the kinases. These ions also interfere with mast cell release of histamine, which is associated with allergic reactions rather than viral causes.

Specific polyvalent ions that can be used are Zn^{2+}, Cu^{2+}, Al^{3+}, Fe^{3+}, Sn^{2+} and Mn^{2+}, either alone or in combination with each other. Calcium has a large diffuse electron cloud, and the other ions have smaller, tighter electron clouds. This allows the other ions to slip into spots in the calcium cascade that calcium occupies, and then displace calcium by the law of mass action. Since the ions bear the correct charge, they remain in the nasopharyngeal area after the dosage form is consumed. The polyvalent ion can be any charged polyvalent ions that fit the receptor site.

Contrary to the Examiner's assertion that the claims are directed to almost 80% of the 103 known elements, the claims are really directed to pharmaceutically acceptable polyvalent ions that fit the receptor site, including organic cations or organo-metallic cations that fit the receptor site, and interrupt the calcium cascade because calcium cannot get to the receptor sites.

The present invention provides a method for administering ions that will block the calcium cascade using the Teorell-Meyer gradient. These ions are administered to swamp the calcium ions that occur naturally in the body and thereby inhibit the formation of histamine.

The present invention is directed to a method for treating immune and auto-immune diseases and conditions which cause secretions and eruptions via the calcium cascade. Included in this group are rhinitis, rashes, hives, blistering eruptions, cold sores, and running sores such as the bulbous form of impetigo.

The Examiner alleges that autoimmune diseases are notoriously difficult to treat. However, the claims are not directed to treating all auto-immune diseases, but to treating only those auto-immune diseases that cause secretions and eruptions via the calcium cascade.

It is respectfully submitted that one skilled in the art would appreciate that interfering with the calcium cascade can interfere with the progress of autoimmune diseases, particularly those involving inflammation.

Submitted herewith are abstracts of articles concerning the involvement of the calcium cascade in autoimmune diseases:

1. Rosignoli et al., *Clin. Exp. Immunol.* 2005 **142(3)**: 411-418. It is well known that the salivary gland secretes less in an autoimmune process, although there is secretion in an autoimmune disease. Zinc or other polyvalent ions would work on the calcium cascade.
2. Liumbruno et al., *J. Clin. Apher.*, Jan. 19, 2006; epub ahead of print. Psoriasis, a well-known autoimmune disease, is caused by the secretion of cytokines from T1 lymphocytes, and is responsive to zinc if the zinc can reach the subcutaneous compartment where the lymphocytes are.
3. Yamamoto et al., *Autoimmune Rev.* 2005 **4(4)**: 195-200. In this case the cascade is overactive.
4. Lopez-Diaz et al., *Am. J. Physiol Gastrointest Liver Physiol*. Jan 6, 2006, epub ahead of print. Parietal cells excrete hydrogen ion because of the calcium cascade, via calmodulin. This is what is affected by polyvalent ions.
5. Wahl et al., *Cells Tissues Organs* 2003; **174(1-2)**: 26-33 NOS isoforms are regulated by calcium fluxes and interaction with calmodulin.

6. Ishikawa et al., *J. Immunol* 2003 **170(9)**: 4441-4449. A calcium ion entry blocker as potent immunomodulator for treating autoimmune diseases.

The following articles also relate the calcium cascade to autoimmune diseases:

1. Liumbruno GM, Centoni PE, Molfettini P, Ceretelli S, Ceccarini M, Bachini L, Pomponi A, Bagnoni G, Vitolo M, Eberle O, Biondi A, Sodini ML, Lymphocytapheresis in the treatment of psoriasis vulgaris, *J Clin Apher*. 2006 Jan 19; [Epub ahead of print]
PMID: 16425186 [PubMed - as supplied by publisher]
2. Lopez-Diaz L, Hinkle KL, Jain RN, Zavros Y, Brunkan CS, Keeley T, Eaton KA, Merchant JL, Chew CS, Samuelson LC, Parietal Cell Hyperstimulation and Autoimmune Gastritis in Cholera Toxin Transgenic Mice, *Am J Physiol Gastrointest Liver Physiol*. 2006 Jan 6; [Epub ahead of print]

PMID: 16399875 [PubMed - as supplied by publisher]

3. Rosignoli F, Roca V, Meiss R, Leceta J, Gomariz RP, Perez Leiros C., Defective signalling in salivary glands precedes the autoimmune response in the non-obese diabetic mouse model of sialadenitis, *Clin Exp Immunol*. 2005 Dec;**142(3)**:411-8, PMID: 16297151 [PubMed - indexed for MEDLINE]

4. Triggiani M, Granata F, Giannattasio G, Marone G., Secretory phospholipases A2 in inflammatory and allergic diseases: not just enzymes, *J Allergy Clin Immunol*. 2005 Nov;**116(5)**:1000-6. Epub 2005 Oct 3. Review.
PMID: 16275367 [PubMed - indexed for MEDLINE]

5. Mouzaki A, Deraos S, Chatzantoni K. Advances in the treatment of autoimmune diseases; cellular activity, type-1/type-2 cytokine secretion patterns and their modulation by therapeutic peptides, *Curr Med Chem*. 2005;**12(13)**:1537-50. Review.
PMID: 15974986 [PubMed - indexed for MEDLINE]

6. Yamamoto M, Takahashi H, Sugai S, Imai K. Clinical and pathological characteristics of Mikulicz's disease (IgG4-related plasmacytic exocrinopathy). *Autoimmun Rev.* 2005 Apr;**4(4)**:195-200. Epub 2004 Nov 17. Review.
PMID: 15893711 [PubMed - indexed for MEDLINE]

7. Rosatelli TB, Roselino AM, Dellalibera-Joviliano R, Reis ML, Donadi EA. Increased activity of plasma and tissue kallikreins, plasma kininase II and salivary kallikrein in pemphigus foliaceus (fogo selvagem), *Br J Dermatol.* 2005 Apr;**152(4)**:650-7.
PMID: 15840094 [PubMed - indexed for MEDLINE]

One skilled in the art noting that the bulbous form of impetigo can be treated by interrupting the calcium cascade would expect that other such diseases which cause secretions *via* the calcium cascade could also be treated successfully.

Claim 12 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

This rejection is respectfully traversed. Claim 12 has been rewritten as newly submitted claim 14 to include a description of the dosage form. This dosage form is that claimed in claim 12 of U.S. Patent No, 6,414,033, which has been incorporated by reference in the present application.

ART REJECTIONS

Claims 1-3 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kashrina in view of Mandell et al.

This rejection is respectfully traversed. Claim 1, and thus claims 2, 3 and 10, has been amended to recite that the method "consists of." That is, nothing is administered other than at least one pharmaceutically acceptable polyvalent metal ion that blocks the calcium cascade. Kashrina, on the other hand, administers a combination of syntomycin/zinc paste. Syntomycin is an antibiotic originally isolated from cultures of *Streptomyces venequelae* in 1947, but is now produced synthetically. It acts by interfering with bacterial protein synthesis and is mainly bacteriostatic. Kashrina applies the paste onto the skin, where it disinfects skin and stops oozing lesions and eliminates hyperemia. There is nothing in either Kashrina or Mandell et al. that would suggest to one skilled in the art that a polyvalent metal salt

alone would be useful in treating impetigo. It is not known which of the components of the Kashrina paste causes these effects, and there is absolutely no recognition of inhibiting the calcium cascade by administering an effective amount of a pharmaceutically acceptable polyvalent metal ion.

In view of the above, it is respectfully submitted that the claims are now in condition for allowance, and favorable action is earnestly solicited.

Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.
Attorneys for Applicant

By: _____
Anne M. Kornbau
Registration No. 25,884

AMK:srd
Telephone No.: (202) 628-5197
Facsimile No.: (202) 737-3528
G:\BN\G\Gels\Sceusa3A\Pto\AMD 13 FEB 06.doc